IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	)	Examiner: Bunner, Bridget E.
Kevin P. BAKER, et al.	)	Art Unit: 1647
Application Serial No. 10/015,822	)	Confirmation No: 8184
Filed: December 10, 2001	)	Attorney's Docket No. GNE-2830-P1C38
For: **PRO1759 POLYPEPTIDES**	)	**Customer No. 77845**

FILED VIA EFS – October 6, 2008

ON APPEAL TO THE BOARD OF PATENT APPEALS AND INTERFERENCES APPELLANTS' REPLY BRIEF

MAIL STOP APPEAL BRIEF - PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

On April 12, 2007, the Examiner made a Final rejection to pending Claims 28-35 and 38-40. A response to Final Office Action was filed on August 13, 2007 and a Notice of Appeal was filed on September 11, 2007. An Advisory Action was mailed November 13, 2007. An Appellants' Appeal Brief was subsequently filed January 10, 2008.

An Examiner's Answer was mailed on August 7, 2008. The following constitutes Appellants' Reply Brief in response to the Examiner's Answer and is timely filed within the period set for response. This Reply Brief is accompanied by a Request for Oral Hearing.

REMARKS / ARGUMENTS

Appellants acknowledge that the claims of the instant application are directed to PRO1759 polypeptides.

I. *Claim Rejections Under 35 U.S.C. §101 and §112, First Paragraph*

Concerning the rejection of Claims 28-35 and 38-40 under 35 U.S.C. §101 as allegedly lacking a specific, substantial and credible asserted utility or a well established utility, in her Answer, the Examiner cites the following arguments:

(1) The instant rejections are primarily based on whether or not genomic DNA levels (as measured by the gene amplification assay) correlate with either mRNA levels or polypeptide levels. The Examiner alleges that the Polakis Declarations filed under 37 CFR 1.132 filed on February 22, 2005 and August 7, 2006 are limited to an issue that is no longer relevant (i.e.: mRNA levels are most likely predictive of polypeptide levels) in the instant case. In addition, the Examiner asserts that the fact pattern in the Board Decision (Appeal No. 2006-1469), where the microarray assay was the issue, differs significantly from the instant gene amplification case. The Examiner alleges that there were several critical pieces of evidence supporting the Appellant's position in the microarray cases; for example, multiple declarations, including high probative declarations containing further data. The Examiner alleges that she does not find such preponderance of evidence in support of the position that increased genomic DNA levels correlate with increased polypeptide levels (pages 33-34 of the Examiner's Answer).

(2) The Examiner did not find the Goddard declaration persuasive and asserts that "it does not speak to whether or not the encoded polypeptides are also found at increased levels in cancerous tissues" since the claims are directed to PRO1759 polypeptides, not PRO1759 genes (Examiner's Answer, page 21). The Examiner addresses the pooled blood controls used in the gene amplification assay and asserts that the controls were not matched, non-tumor lung samples, but rather pooled DNA samples from blood of healthy subjects. The Examiner insists that the art (allegedly, Pennica *et al.*) used matched tissue samples (page 26 of Examiner's Answer). The Examiner asserts that there is no detailed description of the type, class, or stage of any of the tumor samples in which PRO1759 tested positive for gene amplification (page 25 of Examiner's Answer). The Examiner asserts that the data presented in the specification were not

corrected for aneuploidy and cites a reference by Sen *et al.* in support of the assertion that "[a] slight amplification of a gene does not necessarily correlate with overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid." (page 27 of Examiner's Answer).

(3) The Examiner alleges that the Ashkenazi declaration actually supports the Examiner's position in that it provides further evidence that gene amplification does not correlate with increased mRNA/polypeptide levels. (page 23 of the Examiner's Answer)

(4) Regarding the supportive references Orntoft *et al.*, Hyman *et al.* and Pollack *et al.*, made of record by the Appellants, and which clearly address gene amplification, the Examiner considers them flawed. The reasons cited were: Orntoft *et al.* only compared levels of about 40 well-resolved an focused on abundant proteins; Hyman *et al.* found 44% of highly amplified genes showed overexpression at the mRNA level, and 10.5% of highly overexpressed genes were amplified and even at this level of high amplification and high overexpression, the two did not correlate; Pollack *et al.* is also limited to highly amplified genes and used a different method to evaluate their results (pages 17-18 of Examiner's Answer).

(5) The Examiner asserts that references such as Pennica *et al.*, Sen *et al.*, Godbout *et al.*, Bea *et al.* and Li *et al.* constitute strong opposing evidence for the claimed polypeptides having utility and enablement, based on the presumption that the claimed polypeptides are also overexpressed following gene amplification (page 21 of the Examiner's Answer). Referring to Sen, the Examiner alleges that, in general, non-cancerous epithelial tissues are frequently aneuploid, and thus an increase in genomic DNA is not diagnostic of cancer. The Examiner also quotes Godbout as stating: "*It is generally accepted that co-amplified genes are not over-expressed unless they provide a selective growth advantage to a cell...*" and thereby inquires whether Appellant can show evidence for PRO1759 providing a selective growth advantage to a cell (page 22 of Examiner's Answer).

Appellants strongly disagree with each of the Examiner's arguments on a number for grounds. The Examiner's arguments will be addressed in the order they are listed above.

Reply to the Examiner's arguments

(1) and (2) The Goddard Declaration was presented to show what ΔCt values were considered significant in the TaqMan™ assay. The ΔCt values for the DNA that encodes for PRO1759 showed **2.16-2.85 fold amplification in three lung and colon tumors**, which would be considered significant according to the Goddard Declaration. While this declaration addresses DNA values, it has been presented in this polypeptide case in conjunction with several other supportive references like Orntoft et al., Hyman et al., Pollack et al., Bea et al., Godbout et al., etc. As explained previously, Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.* were presented to show that in general, gene amplification increases mRNA expression. In addition, Appellants presented two Polakis Declarations (Polakis I and II) to show that, in general, mRNA levels correlate well with protein levels, and the Examiner seems to agree with this point especially in view of the recent Board Decision (Decision on Appeal No. 2006-1469) addressing microarray cases. Presentation of the Goddard Declaration is indeed relevant in this polypeptide case, because it forms a critical piece of evidence in this case. When placed together with the entire evidence presented for PRO1759, one would logically come to the conclusion that, it is more likely than not, that increased DNA levels generally correlate well with increased mRNA levels (based on, for example, the teachings of supportive references like Orntoft et al., Hyman et al., Pollack et al., Bea et al., Godbout et al., etc.), and further, increased mRNA levels generally correlate well with increased protein levels (the Polakis Declarations and the recent Board decision). In summary, just as in the microarray cases, Appellants have presented multiple pieces of evidence, such as the Goddard Declaration, the Ashkenazi Declaration, two Polakis Declarations, and several references addressing the relationship between DNA and mRNA/ protein levels, etc., each of which is critical evidence that supports their position that PRO1759 polypeptides have utility based on the gene amplification results. Therefore, Appellants believe that a sound case has been presented for utility of PRO1759 as a diagnostic marker, based on the gene amplification data of its corresponding gene in the specification.

Further, the Examiner is required to view the statements in the declaration with the total evidence presented in this case. The case law has clearly established that in considering affidavit evidence, the Examiner must consider all of the evidence of record anew (*In re Rinehart,* 531 F.2d 1084, 189 USPQ 143 (C.c.P.A. 1976); *In re Piasecki, 745*F.2d. 1015,226 USPQ 881 (Fed.

Cir. 1985)). "After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument."(*In re Alton,* 37 USPQ2d 1578, 1584 (Fed. Cir 1996) (quoting *In re Oetiker,* 977 F.2d 1443, 1445,24 USPQ2d 1443, 1444 (Fed. Cir. 1992)). Furthermore, the Federal Court of Appeals held in *In re Alton,* "We are aware of no reason why opinion evidence relating to a fact issue should not be considered by an Examiner (*In re Alton, supra.).* Appellants also respectfully draw the Examiner's attention to the Utility Examination Guidelines (Part IIB, 66 Fed. Reg. 1098 (2001)) which state, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." Appellants submit that the Patent Office has failed to provide substantial evidence for disregarding the contribution of the Goddard Declaration in establishing the significance of the gene amplification data, which is a critical piece of evidence in this case.

Regarding the characterization of the tumor samples in which PRO1759 tested positive for gene amplification, Appellants submit that these tumor samples were acquired from publicly-available tissue banks and one skilled in the art could have determined the detailed description of the type, class, or stage of any of the tumor samples, using the designations provided in the specification.

Regarding the rejection of pooled controls (addressed in the Goddard Declaration), Appellants respectfully submit that the Pennica *et al.* reference does not teach matched controls as the Examiner contends. In fact, Pennica *et al.* teaches the exact same "pooled normal blood controls" as that used in the instant gene amplification assay (for instance, see page 14718, column 1 and Figure 5 of Pennica *et al.*). Further, the references Bieche *et al.* and Pitti *et al.*, submitted as Exhibits F and G with the Goddard Declaration, also used "pooled normal blood controls" as control. For instance, in Pitti *et al.* the authors used the same quantitative TaqMan PCR assay and pooled normal blood controls described in the instant specification, to study gene amplification in lung and colon cancer of DcR3, a decoy receptor for Fas ligand. Pitti *et al.* analyzed DNA copy number "in genomic DNA from 35 primary lung and colon tumors, relative to pooled genomic DNA from peripheral blood leukocytes (PBL) of 10 healthy donors." (Page

701, col. 1). The authors also analyzed mRNA expression of DcR3 in primary tumor tissue sections and found tumor-specific expression, confirming the finding of frequent amplification in tumors, and confirming that the pooled blood sample was a valid negative control for the gene amplification experiments. In Bieche *et al.*, the authors used the quantitative TaqMan PCR assay to study gene amplification of myc, ccnd1 and erbB2 in breast tumors. As their negative control, Bieche *et al.* used normal leukocyte DNA derived from a small subset of the breast cancer patients (page 663). The authors note that "[t]he results of this study are consistent with those reported in the literature" (page 664, col. 2). Thus, contrary to the Examiner's allegations, Pennica *et al,* Pitti *et al.* and Bieche *et al.* in fact, confirm the validity of use of the "pooled blood control" as a negative controls, and indicate that this control was widely utilized in the art at the time of filing of the instant application. Appellants further submit that the Examiner's position is scientifically incorrect because the instant application relies on **genomic DNA** amplification for utility and not cDNA expression. Different types of cells from the same organism should have the same set of genomic DNA. Thus, it does not matter what kind of cells you use for the control as long as the control cells have the entire genome. Accordingly, a "tissue-matched" control is not necessary in the gene amplification assay.

Regarding the data allegedly not being corrected for aneuploidy, Appellants reiterate that it is known in the art that detection of gene amplification can be used for cancer diagnosis regardless of whether the increase in gene copy number results from intrachromosomal changes or from chromosomal aneuploidy. As explained by Dr. Ashkenazi in his Declaration (submitted with Appellants' Response filed February 2, 2005),

> An increase in gene copy number can result not only from intrachromosomal changes but also from chromosomal aneuploidy. It is important to understand that detection of gene amplification can be used for cancer diagnosis even if the determination includes measurement of chromosomal aneuploidy. Indeed, as long as a significant difference relative to normal tissue is detected, it is irrelevant if the signal originates from an increase in the number of gene copies per chromosome and/or an abnormal number of chromosomes.

Hence, Appellants submit that gene amplification of a gene, whether by aneuploidy or any other mechanism, is useful as a diagnostic marker.

Regarding the art exemplified by Sen *et al.*, Appellants maintain their position that this reference still supports their case for the reasons outlined in their Appeal Brief filed January 10,

2008, which is hereby incorporated by reference. Briefly Appellants maintain that, even if the amplification of the PRO1759 gene were due to chromosomal aneuploidy (which Appellants expressly do not concede to), since there is utility for an aneuploid gene at least as a marker for cancer or precancerous cells or damaged tissue, one skilled in the art would find it entirely reasonable that PRO1759 is useful in the early detection of lung and colon cancer.

Appellants further note that the Examiner seems to be applying a heightened utility standard in this instance, which is legally incorrect. Appellants have shown that the gene encoding PRO1759 was significantly amplified, from 2.16-fold to 2.85-fold, in 3 lung and colon tumors. These values are considered significant based on the Declaration by Dr. Audrey Goddard discussed above. By referring to the 2.16-fold to 2.85-fold amplification as "slight," the Examiner appears to ignore the teachings within an expert's declaration without any basis, or without presenting any evidence to the contrary. Appellants also emphasize that they have shown significant DNA amplification in three of the lung tumor samples in Table 8, Example 143 of the instant specification. The fact that not all lung and colon tumors tested positive in this study does not make the gene amplification data less significant. As any skilled artisan in the field of oncology would easily appreciate, not all tumor markers are generally associated with every tumor, or even, with most tumors. For example, the article by Hanna and Mornin (of record), discloses that the known breast cancer marker HER-2/neu is "amplified and/or overexpressed in 10%-30% of invasive breast cancers and in 40%-60% of intraductal breast carcinoma" (page 1, col. 1). In fact, some tumor markers are useful for identifying rare malignancies. That is, the association of the tumor marker with a particular type of tumor lesion may be rare, or, the occurrence of that particular kind of tumor lesion itself may be rare. In either event, even these rare tumor markers which do not give a positive hit for most common tumors, have great value in tumor diagnosis, and consequently, in tumor prognosis. The skilled artisan would certainly know that such tumor markers are useful for better classification of tumors. Therefore, whether the PRO1759 gene is amplified in two lung tumors or in all lung tumors is not relevant to its identification as a tumor marker, or its patentable utility. Rather, the fact that the amplification data for PRO1759 is considered significant is what lends support to its usefulness as a tumor marker.

(3) The Examiner alleges that the Ashkenazi Declaration actually supports the Examiner's position in that it provides further evidence that gene amplification does not correlate with increased mRNA/polypeptide levels. This position of the Examiner is based on a complete misinterpretation of the Ashkenazi Declaration, its teachings and the arguments presented by the Appellants regarding this Declaration. Appellants fail to see how the Ashkenazi Declaration could support the Examiner's arguments when Appellants clearly stated that, even if there were no correlation between gene amplification and increased mRNA/protein expression, (**which Appellants expressly do not concede to**), a polypeptide encoded by a gene that is amplified in cancer would still have a specific, substantial, and credible utility. Appellants submit that, based on the teachings of the Ashkenazi Declaration and the Hanna and Mornin reference (both previously made of record), one of skill in the art would have known that simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, were not to be over-expressed. This leads to better determination of a suitable therapy for the tumor, as demonstrated by a real-world example of the breast cancer marker HER-2/neu. Again, the presentation of this explanation in support of utility is not to be interpreted as a submission of a lack of correlation between DNA and/or mRNA/ protein levels.

(4) The Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, Bea *et al.*, and Godbout *et al.* references were presented during prosecution to show that, in general, gene amplification increases mRNA expression. As Appellants have acknowledged, the correlation between changes in mRNA level and protein level is not exact, and there are exceptions (*see, e.g.*, abstracts submitted in the IDS filed on August 7, 2006 as Exhibit 21). However, Appellants have submitted with their Preliminary Amendment of August 7, 2006 over 100 references in addition to the declarations and references already of record which support Appellants' asserted utility, either directly or indirectly. This included references that studied single genes or gene families, multiple or large families of genes, and included studies that a wide variety of techniques, including gene amplification and microarray. Regardless of the techniques employed, **by and large**, increased gene levels generally correlated well with increased mRNA and /or protein levels, even if accurate predictions of proteins could not be made. As discussed

throughout prosecution, the law does not require the existence of a "necessary" correlation between DNA/mRNA and protein levels, or that protein levels be "accurately predicted." In fact, authors in several of the cited references (cited both, by the Examiner, and by Appellants) themselves acknowledge that there is a general correlation between protein expression and transcript levels and DNA levels, which meets the "more likely than not standard." Therefore Appellants have explored this issue thoroughly throughout prosecution in the vast number of references presented in this case and the evidence should be viewed as a whole.

Regarding the Examiner's contention that references Orntoft *et al.*, Hyman *et al.*, Pollack *et al.* are flawed because, allegedly, their studies were directed to highly amplified genes or abundant proteins, Appellants have submitted that PRO1759 is significantly amplified (according to the Goddard Declaration) throughout prosecution. Appellants believe that this significantly amplified DNA would more likely than not result in a higher expression of PRO1759 protein, according to the teachings of many references including Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, Bea *et al.*, Godbout *et al.*

(5) Appellants have already discussed the references Pennica *et al.*, Sen *et al.*, Godbout *et al.*, Bea *et al.* and Li *et al.* in great detail throughout prosecution and in their Appeal Brief filed January 10, 2008; these discussions and arguments are hereby incorporated by reference.

Briefly, the teachings of Pennica *et al.* are specific to *WISP* genes, a specific class of closely related molecules. Pennica *et al.* showed that there was good correlation between DNA and mRNA expression levels for the *WISP-1* gene but not for *WISP-2 and WISP-3* genes. The fact that, for two out of three specific molecules there seems to be no correlation between gene amplification and/or mRNA/protein expression, does not establish that it is more likely than not, in general, that such correlation does not exist. As discussed throughout prosecution, the standard is not absolute certainty. Pennica *et al.* has no teaching whatsoever about the correlation of gene amplification and protein expression for genes in general. Indeed, the working hypothesis among those skilled in the art is that, if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level. In fact, as noted even in Pennica *et al.*, "[a]n analysis of *WISP*-1 gene amplification and expression in human colon tumors *showed a correlation between DNA amplification and over-expression* . . . " (Pennica *et al.*, page 14722, left column,

first full paragraph, emphasis added). Accordingly, Appellants respectfully submit that Pennica *et al.* teaches nothing conclusive regarding the absence of correlation between gene amplification and over-expression of mRNA or polypeptides in most genes, in general. Therefore, the teachings of Pennica *et al.* are not directed towards genes in general but to a single gene or genes within a single family and thus, their teachings cannot support a general conclusion regarding a correlation between gene amplification and mRNA or protein levels.

In fact, in the majority of amplified genes, the teachings in the art, as exemplified by Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Appellants submit that when the proper legal standard is applied, one of skill in the art should reach the conclusion, based on the amplification data for the PRO1759 gene, that the PRO1759 polypeptide is concomitantly overexpressed, and that the present application discloses at least one patentable utility for the claimed PRO1759 polypeptides. Accordingly, one of ordinary skill in the art would also understand how to make and use the recited polypeptides for the diagnosis of lung and colon cancer without any undue experimentation.

Regarding the art exemplified by Sen *et al.*, Appellants' maintain their position that Sen still supports their case for the reasons outlined in their Appeal Brief filed January 10, 2008, which is hereby incorporated by reference. Briefly Appellants maintain that, even if the amplification of the PRO1759 gene were due to chromosomal aneuploidy (which Appellants expressly do not concede to), since there is utility for an aneuploid gene at least as a marker for cancer or precancerous cells or damaged tissue, one skilled in the art would find it entirely reasonable that PRO1759 is useful in the early detection of lung and colon cancers.

The Examiner contends that the Li article constitutes strong opposing evidence for the presumption that the claimed polypeptides are also overexpressed following gene amplification. Appellants respectfully disagree. The Li article was discussed extensively in the Appeal Brief filed January 10, 2008; these discussions and arguments are hereby incorporated by reference. In the article, genes were considered to be amplified if they had a copy number ratio of at least 1.40. In the instant case for PRO1759, as discussed in the Goddard Declaration (of record), an appropriate threshold for considering gene amplification to be significant is a copy number of at least 2.0 (which is a higher threshold that Li's 1.40). The PRO1759 gene showed significant

amplification of **2.16-2.85 fold amplification in three lung and colon tumors**, and thus fully meets the Goddard standard as well as the Li standard. Appellants further note, and it is not surprising that, in the Li *et al.* reference, by using a lower threshold of 1.4 for considering gene amplification, a higher number of genes not showing corresponding increases in mRNA expression were found. Nevertheless, the results of Li *et al.* do not conclusively disprove that a gene with a substantially higher level of gene amplification, such as PRO1759, would be expected to show a corresponding increase in transcript expression. Therefore Li does not constitute opposing evidence.

In response to Appellants' argument that the discordance may reflect methodologic differences, the Examiner asserts that "Li *et al.* did not limit their studies to genes that were amplified at less than 2-fold." In support of this assertion, the Examiner cites the first paragraph of the Supplemental Material. (Pages 31-32 of the Examiner's Answer). Appellants respectfully point out that the Examiner has misinterpreted the methodology disclosed in the supplemental material. The evidence cited by the Examiner pertains to the inclusion criteria of the probes used for defining amplicons. In the second paragraph entitled "Relationship between genomic copy number and gene transcript level", the authors state that "[f]or each gene, the CGH data were represented by a vector that was labeled '1' for genomic overrepresentation (including amplification) ratio greater than 1.40 and '0' for no genomic overrepresentation." Nevertheless, the Examiner acknowledges that the alleged 2-fold amplification criteria would only apply to some of the samples. The Examiner has not established that a correlation does not exist in samples based solely on this threshold.

Based on Godbout et al., the Examiner requests "that the protein encoded by the PRO1759 gene would confer any selective advantage on a cell expressing it." in the Examiner's answer; in other words, the Examiner requests Appellants to show the mechanism by which the claimed protein acts within the cell. However, Appellants respectfully remind the Board that demonstration of the mechanism is not a requirement for attaining that utility. Appellants believe that such a requirement is a heightened utility standard imposed by the Examiner. In fact, as stated by the Federal Circuit, "it is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works." *In re Cortwright*, 165 F.2d 1353, 1359 (Fed. Cir. 1999). The Federal Circuit has also stated that "[a]n invention need not be

the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is not operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.* 730 F.2d 753,762, 221 USPQ 473,480 (Fed. Cir. 1984)." Hence this rejection is improper.

Collectively, Appellants submit that the Examiner's concerns in this rejection are misplaced and cannot properly form the basis for utility rejections of the present claims.

Claim Rejections Under 35 U.S.C. §112, First Paragraph - Enablement

Claims 28-35 and 38-40 stand rejected under 35 U.S.C. §112, first paragraph, for containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains or with which it is most nearly connected, to make and/or use the invention.

Appellants disagree for the reasons previously presented in Appellants Brief and in the discussion presented herein under Claim Rejections under 35 USC §101. Appellants submit that, as discussed above, antibodies to the PRO1759 polypeptides have utility in the diagnosis of colon and lung cancer. Based on such a utility, one of skill in the art would know exactly how to use the claimed polypeptides, for example, for diagnosis of cancer without any undue experimentation.

Claim Rejections Under 35 U.S.C. §112, First Paragraph – Written Description

Claims 28-32 and 39-40 stand rejected under 35 U.S.C. §112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Appellants disagree for the reasons previously presented in Appellants Brief filed January 10, 2008. Appellants maintain that, based on the ample disclosure in the specification, one skilled in the art would have known that Appellants had knowledge and possessed the claimed polypeptides with 80-99% sequence identity to SEQ ID NO: 374 whose encoding nucleic acids were amplified in colon and lung tumors. The recited property of amplification of the encoding gene adds to the characterization of the claimed polypeptide sequences in a manner that one of

skill in the art could readily assess and understand. As discussed previously, Appellants have recited structural features, namely 80-99% sequence identity to SEQ ID NO: 374, which are common to the genus. Appellants have also provided guidance as to how to make the recited variants of SEQ ID NO: 374, including listings of exemplary and preferred sequence substitutions. The genus of claimed polypeptides is further defined by having a specific functional activity for the encoding nucleic acids. Accordingly, a description of the claimed genus has been achieved.

CONCLUSION

For the reasons given above, Appellants submit that present specification clearly describes, details and provides a patentable utility for the claimed invention. Moreover, it is respectfully submitted that based upon this disclosed patentable utility, the present specification clearly teaches "how to use" the presently claimed polypeptides. As such, Appellants respectfully request reconsideration and reversal of the outstanding rejection of Claims 28-35 and 38-40.

The Commissioner is authorized to charge any fees which may be required, including extension fees, or credit any overpayment to Deposit Account No. **50-4634** (referencing Attorney's Docket No. **123851-181898 GNE-2830 P1C38**).

Respectfully submitted,

Date: October 7, 2008

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